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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/834,321	04/13/2001	Jeffrey V. Ravetch	TRU-0005	2584

7590 10/22/2002

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EXAMINER

BELYAVSKIY, MICHAIL A

ART UNIT	PAPER NUMBER
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1644

DATE MAILED: 10/22/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/834,321

Applicant(s)

RAVETCH, JEFFREY V.

Examiner

Michail A Belyavskyi

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 July 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 3,5-9 and 16-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,4, and 10-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 13 April 2001 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4-6. 6) ☐ Other: _____

DETAILED ACTION

1. *Claims 1-21 are pending.*

2. Applicant's election with traverse of Group II, Claims 1-2, 4 and 10-15 in Paper No. 8 and a specific antibody which binds a Her2/neu growth factor, are acknowledged. Applicant traverse the Restriction Requirement on the grounds that the search of Groups I-, II, IV and V together would not constitute a serious search burden on the examiner. This is not found persuasive because the MPEP 803 (August 2001) states that "For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search". The Restriction Requirement enunciated in the previous Office Action meets this criterion and therefore establishes that serious burden is placed on the examiner by the examination Groups. The Inventions are distinct for reasons elaborated in paragraphs 3-7 of the previous Office Action, filed on 03/07/02, Paper No. 7.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-2, 4, 10-12 and 14-15 read on the elected species of specific antibody which binds a Her2/neu growth factor. Since the elected species was found to be free of prior art, the prior art search was extended to include antibody which binds CD20 B cell antigen recited in Claim 13.

3. Claims 3, 5-9 and 16-21 (non-elected groups I, III-VI) are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 1-2, 4 and 10-15, drawn to a method for enhancing cytotoxicity with an antibody, wherein the antibody are specific for a HER2/neu growth factor receptor or for CD20 B cell antigen are under consideration in the instant application.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed*.

5. The use of the trademark HERCEPTIN (page 5, line 8 of the specification as filed), RITUXAN (page 5, line 11 of the specification as filed) and Silastic RTM (page 27, line 29 of the

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specification as filed) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

6. Formal drawings have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

A. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability."

Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

B. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in ABANDONMENT of the application.

7. Applicant's IDS, filed on 09/07/01 is acknowledge. References marked with an asterisk (*) crossed out on the PTO 1449 form have not been considered, because they were not provided by Applicant.

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8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-2, 4, and 10-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

The claims as written encompass the genus of antibodies that have a reduced binding affinity for FcRIIB, due to modification of the Fc portion of the antibody, while retaining or enhancing binding to FcRIIA and Fc RIIIA and use them in a method for enhancing cytotoxicity elicited by a this antibody *in vivo*, which method comprises disrupting activation of SHIP by Fc RIIB.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

There is insufficient guidance and direction as to how to make an antibody that have a reduced binding affinity for FcRIIB, due to modification of the Fc portion of the antibody, while retaining or enhancing binding to FcRIIA and Fc RIIIA and use them in a method for enhancing cytotoxicity elicited by antibody *in vivo*, which method comprises disrupting activation of SH2 domain containing inositol 5-phosphatase (SHIP) by FcRIIB.

The specification disclosed that FcRII B makes a dominant contribution to antibody-mediated cytotoxicity and that disrupting RcRII greatly improves cytotoxicity (page 8, lines 10-15). The specification also disclosed that to practice the invention it would be essential that antibodies, while reducing their binding affinity for FcRIIB, due to modification of the Fc portion of the antibody, still retaining or enhancing binding to FcRIIA and FcRIIIA (page 7, lines 10-15 of specification as filed). However, the specification does not provide sufficient guidance and

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examples as to which modifications would be acceptable to retain these specific structural and functional properties of claimed antibodies to be used in the claimed method for enhancing cytotoxicity elicited by antibody *in vivo*, which method comprises disrupting activation of SHIP by FcRIIB. In addition, the term "modifying" encompass any substitution, deletion or insertion (page 14, lines 13-16 of Specification as filed) of Fc portion of the antibody that will affect their structural and functional properties.

Applicant acknowledges that single amino acid replacement in Fc portion of the mouse anti-HER2 antibody 4D5 reduces affinity for **both** FcRII and FcRIII receptors (page 35, lines 5-20 of the Specification as filed). Moreover, Colman *et al.*, in *Research in Immunology* (145(1):33-36, 1994) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Abaza *et al.*, in *Journal of Protein Chemistry* (11(5):433-444, 1992) teach that single amino acid substitutions outside the antigenic site on a protein effect antibody binding. Further, Lederman *et al* in *Molecular Immunology* (28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Additionally, Li *et al* in *PNAS* (77:3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document).

Because of this lack of guidance, an undue experimentation would be required to determine which modifications would be acceptable to retain occluding structural and functional activity, and the fact that the relationship between the sequence of a protein/peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo *et al* in the *Protein Folding problem and Tertiary Structure prediction*, 1994, Merz *et al.*, (ed), Birkhauser, Boston, MA, pp.433 and 492-495), it would require an undue amount of experimentation for one of skill in the art to arrive at the claimed method for enhancing cytotoxicity elicited by a therapeutic antibody *in vivo*, which method comprises disrupting activation of SHIP by Fc RIIB encompassed by the claimed invention.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed method for enhancing cytotoxicity elicited by a therapeutic antibody *in vivo*, which method comprises disrupting activation of SHIP by Fc RIIB in manner reasonably correlated with the scope of the claims. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, lack of working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

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10. Claims 1-2, 4, and 10-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims as written encompass the genus of antibodies that have a reduced binding affinity for FcRIIB , due to modification of the Fc portion of the antibody , while retaining or enhancing binding to FcRIIA and Fc RIIIA that can be used in a method for enhancing cytotoxicity elicited by a this antibody *in vivo*, which method comprises disrupting activation of SHIP by Fc RIIB .

However, there does not appear to be an adequate written description in the specification as-filed how to make an antibody that have a reduced binding affinity for FcRIIB , due to modification of the Fc portion of the antibody , while retaining or enhancing binding to FcRIIA and Fc RIIIA and use them in a method for enhancing cytotoxicity elicited by antibody *in vivo*, which method comprises disrupting activation of SH2 domain containing inositol 5-phosphatase (SHIP) by FcRIIB .

Applicant has not disclosed any specific antibodies that have a reduced binding affinity for FcRIIB , due to modification of the Fc portion of the antibody , while retaining or enhancing binding to FcRIIA and Fc RIIIA that was used in a method for enhancing cytotoxicity elicited by a this antibody *in vivo*, which method comprises disrupting activation of SHIP by Fc RIIB encompassed by the claimed invention. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

A description of a genus of antibodies may be achieved by means of a recitation of a representative number of antibodies falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly & Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

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Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

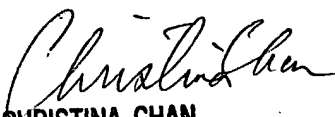
11. No claim is allowed.

12. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Michail Belyavskyi, Ph.D.
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October 21, 2002


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